

REMARKS

Claims 87-116 are pending in this application. In view of its withdrawal from consideration, claim 89 has been canceled without prejudice to Applicants' right to pursue the subject matter of the canceled claim in a related application. Claims 117 and 118 have been added to more particularly point out what Applicants regard as the invention. In order to expedite the prosecution of the application and without conceding to the validity of the Examiner's rejections, claims 87, 88, 90, 91, 102, 107 and 108 have been amended to more particularly point out what Applicants regard as the invention. In particular, claims 87, 88, 90, and 91 have been amended to insert the phrase "numbered according to the EU index as in Kabat," and claims 87 and 91 have been amended to specify that at least one of the amino acid substitutions is at amino acid residue 252, 254, 256, 309, 311, 433 or 434. Claims 87, 88, 90, 91, and 102 have been amended to recite substitution with "glutamic acid" and "aspartic acid" at position 256, and "histidine, phenylalanine, or tyrosine" at position 434, as appropriate. Applicants note that the previous claim terms "glutamate" and "aspartate" are equivalent terms for "glutamic acid" and "aspartic acid." In addition, "lysine" has been deleted from the group of possible amino acid substitutions at position 433 in claims 87, 90 and 91. Further, "alanine" and "asparagine" have been deleted from the group of possible amino acid substitutions at position 256 in claims 87 and 102. Support for the amendments to claims 87, 88, 90, 91 and 102 is found in the specification, *inter alia*, at page 4, lines 32-35; at page 6, lines 25-26; and at page 7, lines 6-7. The amendments are fully supported by the specification of the present application and do not constitute new matter. Upon entry of this Amendment, claims 87, 88, and 90-118 will be pending and under examination.

Applicants thank the Examiner for granting an interview with Applicants' attorneys on February 23, 2005. The Examiner's comments were taken into consideration in drafting this response. The substance of the interview is discussed throughout the Amendment. The amendments and remarks made herein are designed to place the application into condition for allowance. As such, Applicants respectfully request that the amendments and remarks made herein be entered into the record of the application and fully considered by the Examiner.

1. FORMALITIES

The Examiner has withdrawn claim 89 as allegedly directed to a nonelected invention. In response, Applicants have canceled claim 89.

2. THE REJECTIONS UNDER 35 U.S.C. §112, SECOND PARAGRAPH, SHOULD BE WITHDRAWN

Claims 87, 88 and 90-116 are rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to point out and distinctly claim the subject matter which Applicants regard as the invention. Specifically, the Examiner contends that the recitation of amino acid positions in the claims without providing a sequence identification number is indefinite and ambiguous. In the February 23, 2005 interview, the Examiner stated that it was the policy of the Patent Office to require a sequence identifier in any claim referring to particular amino acid residues. The Examiner maintained his view that strict adherence to this policy was required, notwithstanding the Examiner's acknowledgment that immunoglobulins represent a special case where the art has developed a uniform common numbering scheme that is applicable to all immunoglobulin proteins, i.e., the Kabat numbering system. Applicants respectfully maintain that the reference in the claims to particular amino acid residues of an IgG constant domain *numbered according to the EU index as in Kabat* is clear and definite for the reasons of record and for the additional reasons set forth in greater detail below.

The independent claims 87, 88, and 90 recite, in relevant part, a modified IgG comprising a human IgG constant domain comprising one or more amino acid substitutions relative to a wild-type human IgG constant domain at one or more amino acid residues at specified amino acid positions, *numbered according to the EU index as in Kabat*. Independent claim 91 recites, in relevant part, a modified IgG comprising a non-human IgG constant domain comprising one or more amino acid substitutions relative to a wild-type non-human IgG constant domain at one or more amino acid residues at specified amino acid positions, *numbered according to the EU index as in Kabat*.

As indicated in the specification at page 4, lines 32-35, all residues of the IgG constant domain are numbered according to the Kabat numbering system and as presented in Figure 2 (SEQ ID NO: 83). The Kabat numbering system is described in Kabat et al. 1991,

Sequences of Proteins of Immunological Interest, Fifth Edition, NIH Publication No. 91-3242 (hereinafter, "Kabat"). The Kabat system was known in the art at the time of filing this application, as demonstrated by Johnson and Wu, 2000, attached hereto as **Exhibit A**, which refers to the "now-known Kabat numbering system" in the Abstract at page 214.

Importantly, the Kabat numbering system is not based on any one particular sequence. Instead, it is based on a global sequence alignment derived from the alignment of many individual immunoglobulin sequences (see, e.g., the selected pages from Kabat attached hereto as **Exhibit B**). The result is a numbering system that is applicable to all immunoglobulin sequences. Applicants maintain that any given immunoglobulin sequence can be numbered according to Kabat using methods of ordinary skill in the art at the time of filing, for example, using the sequences and tools provided by the Kabat database (see e.g., Johnson and Wu, p. 214, col. 2). In order to exemplify this numbering system and underscore how it is used to reference particular amino acid residues in a sequence, Applicants refer the Examiner to pages 679-87 of Kabat, attached in Exhibit B, which depict the Kabat numbering for the human IgG1 heavy chain constant region CH2. The table lists the constant domain amino acid positions 243-359 according to the Kabat, the EU index, and the OU index in the first three columns. The fourth column gives the identity and location of the amino acid residues that were invariant over the aligned sequences. The next 159 columns give the amino acid residue at each of amino acid positions 243-359 for 159 aligned sequences. Finally, the final four columns provide certain statistics for the alignment at each position. It is clear from this table that each position numbered according to Kabat refers to a definite amino acid in the alignment. Applicants maintain that the identity of the particular amino acid at any position can be determined for any aligned immunoglobulin sequence using methods that were publicly available and within the routine skill in the art at the time of filing this application.

In summary, Applicants maintain that each position in a sequence numbered according to Kabat has a clear and definite meaning to one of skill in the art. Therefore, the recitation of particular amino acid residue positions, numbered according to the EU index as in Kabat, in claims 87-91 is clear and definite without reference to a particular sequence. In response to the Examiner's statements regarding Patent Office policy, Applicants point out that the Office has recently issued a number of patents with claims which reference particular amino acid positions in immunoglobulin sequences according to Kabat without providing a

sequence identifier (see e.g., U.S. Patent Nos. 6,528,624, 6,538,124 and 6,737,056 made of record in Applicants' Supplemental Information Disclosure Statement filed herewith). Accordingly, Applicants respectfully assert that claims 87, 88 and 90-116 satisfy the requirements of 35 U.S.C. §112, second paragraph, and respectfully request that the Examiner's rejection be withdrawn.

The Examiner also rejected claim 107 as allegedly indefinite and ambiguous for reciting "the heavy and light chain variable domain of palivizumab" without reciting a sequence identifier. The Examiner stated in the February 23, 2005 interview that amending the claim to recite the appropriate sequence identifiers would overcome this rejection.

In response, Applicants maintain that the claim is clear and definite because the sequence of the heavy and light chain variable domain of palivizumab was known in the art at the time the subject application was filed. For example, the sequence is described in Johnson et al., J. Infectious Disease 176:1215-24, 1997, which is incorporated by reference in the specification at page 8, lines 5-6, and which was made of record in the Information Disclosure Statement previously filed in connection with this application. However, in order to expedite the prosecution of this application, and in accordance with the Examiner's recommendation, Applicants have amended claim 107 to recite the appropriate sequence identifiers. Support for this amendment is found in the specification at Table III on page 27 which provides the VH and VL domain sequence identifiers for SYNAGIS®. Applicants maintain that SYNAGIS® was known in the art as the commercial name for palivizumab (see e.g., remarks below and the 2001 Physician's Desk Reference entry for SYNAGIS® enclosed as **Exhibit D**).

**3. THE REJECTIONS UNDER 35 U.S.C. §112,
FIRST PARAGRAPH, SHOULD BE WITHDRAWN**

Claim 107 is rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains to make and/or use the invention. Specifically, the Examiner has required that Applicants demonstrate that SYNAGIS® is and was commercially available at the time the application was filed. The Examiner noted that Applicants' Exhibit A, which purported to demonstrate this, was not enclosed with Applicants' Amendment filed September 7, 2004. The Examiner stated in the February 23,

2005 interview that a copy of the appropriate pages showing the entry for SYNAGIS® from the Physicians' Desk Reference would overcome this rejection.

In response, Applicants note that their return receipt postcard bearing the date stamp of September 7, 2004 from the Patent Office lists as item No. 7: "Exhibit A, SYNAGIS® product information from the 2001 and 2004 Physicians' Desk Reference." A copy of the postcard is attached hereto as **Exhibit C**. Accordingly, Applicants maintain that Exhibit A was enclosed with their September 7, 2004 Amendment. However, in order to expedite the prosecution of this application, Applicants enclose herewith as **Exhibit D** a copy of the Exhibit A that was enclosed with their September 7, 2004 response. Applicants maintain that Exhibit D demonstrates that palivizumab is the generic name of SYNAGIS® and that SYNAGIS® was known and commercially available as of the effective filing date of the subject application. Accordingly, Applicants maintain that claim 107 satisfies the requirements of 35 U.S.C. §112, first paragraph, and respectfully request that the Examiner withdraw this rejection.

4. THE REJECTIONS UNDER 35 U.S.C. §102 SHOULD BE WITHDRAWN

Claims 87, 92, 93, 95, 96, and 108-116 are rejected under 35 U.S.C. §102(e) as allegedly anticipated by U.S. Patent No. 6,277,375 ("the Ward patent"). Specifically, the Examiner contends that the Ward patent does teach "amino acid substitution with threonine at amino acid residues 252, 254, or 256 of an IgG," and therefore, anticipates the claimed invention. In the February 23, 2005 interview, the Examiner conceded that Applicants' argument, set forth below, was persuasive and that the rejections under 35 U.S.C. §102(e) should be withdrawn.

In order to anticipate the claimed invention, a single reference must teach each and every element of the claims. Verdegaal Bros. v. Union Oil Co., 814 F.2d 628 (Fed. Cir. 1987). Applicants maintain that the Ward patent does not teach each and every element of claim 87. Specifically, the Ward patent does not teach the particular amino acid substitutions at positions 252, 254, and 256 that are recited in claim 87. For example, the Ward patent does not teach a substitution at position 252 with tyrosine, phenylalanine, tryptophan or threonine. Nor does the Ward patent teach a substitution at position 254 with threonine or a substitution at position 256 with serine, arginine, glutamine, glutamate, aspartate, alanine, asparagine or threonine.

Importantly, while the Ward patent teaches threonine at positions 252, 254, and 256, the Ward patent does not teach a *substitution* of some other residue at position 252, 254, or 256 *with threonine* (see col. 3, lines 39-46). Instead, the Ward patent teaches only the substitution *of threonine* at position 252, 254, or 256 *with other residues*, none of which are the residues recited in claim 87 of the subject application. Specifically, the Ward patent teaches substitution *of threonine* at 252 *with leucine*; substitution *of threonine* at 254 *with serine*; and substitution *of threonine* 256 *with phenylalanine* (see col. 3, lines 56-64).

In view of the fact that the Ward patent does not teach the specific amino acid substitutions at positions 252, 254, and 256 recited by claim 87, Applicants maintain that the Examiner's rejection of claim 87 as anticipated by Ward is improper and respectfully request that the rejection be withdrawn. Likewise, Applicants respectfully request the withdrawal of the rejection of claims 92, 93, 95, 96, and 108-116 under 35 U.S.C. § 102(e), each of which depends from claim 87.

5. THE REJECTIONS UNDER 35 U.S.C. §103 SHOULD BE WITHDRAWN

Claims 106 and 107 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over U.S. Patent No. 6,277,375 ("the Ward patent") in view of U.S. Patent No. 6,572,856 ("the Taylor patent"). Specifically, the Examiner contends that it would have been obvious for one of skill in the art to combine the teachings of the Ward patent with the teachings of the Taylor patent in order to arrive at the invention of claims 106 and 107. In the February 23, 2005 interview, the Examiner conceded that Applicants' argument, set forth below, was persuasive and that the rejections under 35 U.S.C. §103 should be withdrawn.

To establish a *prima facie* case of obviousness, the Examiner must demonstrate three things with respect to each claim. In re Vaeck, 947 F.2d 488 (Fed. Cir. 1991). First, that the cited references, when combined, teach or suggest every element of the claim. Second, that one of ordinary skill would have been motivated to combine the teachings of the cited references at the time of the invention. Third, that there would have been a reasonable expectation that the claimed invention would succeed.

Applicants maintain that the cited references fail to support a *prima facie* case of obviousness because the Taylor patent does not overcome the deficiency of the Ward patent in failing to teach the specific amino acid substitutions at positions 252, 254, and 256 recited

in claim 87, from which claims 106 and 107 depend. Thus, the cited references combined fail to teach each and every element of the claims. Given this failure, Applicants also maintain that in view of such references, neither a motive to combine nor a reasonable expectation of success can exist. Accordingly, Applicants maintain that claims 106 and 107 are not *prima facie* obvious over the Ward patent in view of the Taylor patent and respectfully request that the Examiner withdraw this rejection.

6. THE REJECTIONS UNDER 35 U.S.C. §112, FIRST PARAGRAPH, SHOULD BE WITHDRAWN

Claims 87, 91, 93, 94, and 95-116 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Specifically, the Examiner contends that the claims lack support in the specification as originally filed for the following:

- (i) In claims 87, 91, and 102: substitution at amino acid residue
252 with threonine;
256 with aspartate, alanine, or asparagine;
433 with isoleucine, proline, or glutamine; and
434 with histidine, asparagine, arginine, threonine, lysine or methionine;
- (ii) In claims 93, 94, and 103: substitution at amino acid residue
385 with threonine, histidine, lysine, alanine or glycine;
386 with aspartic acid, serine, lysine, arginine, isoleucine, or methionine; and
387 with proline, histidine, serine, threonine, or alanine;
- (iii) a modified IgG as recited in claims 96, 98, and 99-101; and
- (iv) a modified IgG which has the heavy and light chain of palivizumab as recited in claim 107.

In the February 23, 2005 interview, Applicants advised the Examiner that they would provide support from the specification for the amino acid substitutions recited in the claims. Accordingly, Applicants respectfully traverse the Examiner's rejection and maintain that the claims are fully supported by the specification as originally filed. Applicants note that claims 87, 91, and 102 have been amended to recite substitution with "aspartic acid" at amino acid position 256 and "histidine, phenylalanine, or tyrosine" at amino acid position 434. Further, Applicants note that claims 87 and 102 have been amended to delete substitution with alanine or asparagine at amino acid position 256.

Applicants point to the following support in the specification for the amino acid substitutions recited in claims 87, 91, 102, 93, 94, and 103:

<u>Substitution at:</u>	<u>With:</u>	<u>Specification</u>
252	threonine:	p. 6, <i>ll.</i> 23-24; p. 15, <i>ll.</i> 33-34
256	aspartic acid, alanine, or asparagine:	p. 6, <i>ll.</i> 25-27; p. 15, <i>l.</i> 36 to p. 16, <i>l.</i> 1
433	isoleucine, proline, or glutamine:	p. 7, <i>ll.</i> 5-6; p. 16, <i>ll.</i> 8-9
434	histidine, phenylalanine, or tyrosine:	p. 7, <i>ll.</i> 6-7; p. 16, <i>l.</i> 10
385	threonine, histidine, lysine, alanine, or glycine:	p. 7, <i>ll.</i> 16-17; Table I, p. 19; p. 16 <i>ll.</i> 16-17
386	aspartic acid, serine, lysine, arginine, isoleucine, or methionine:	p. 7, <i>ll.</i> 17-19; p. 16, <i>ll.</i> 17-19
387	proline, histidine, serine, threonine, or alanine:	p. 7, <i>ll.</i> 19-20; p. 16, <i>ll.</i> 19-20

Support for the recitation of the particular IgG isotype IgG₁, IgG₂, IgG₃ and IgG₄ in claims 96, 99, 100, and 101 is found in the specification at page 20, lines 5-6. Support for the recitation of the particular IgG isotypes IgG₁, IgG_{2a}, IgG_{2b}, IgG_{2c} and IgG₃ in claim 98 is found in the specification at page 20, line 7.

Finally, in response to the Examiner's rejection of claim 107 for recitation of the term "palivizumab", Applicants point out that "palivizumab" is a generic term for SYNAGIS®, which is described in the specification at page 8, lines 2-5. Applicants maintain that it is proper to use the generic term instead of the trademark name in the claim since the trademark is used to identify a source of goods, not the goods themselves. In fact, the use of a trademark name as a limitation of a claim is improper according to M.P.E.P. §2173.05(u). Since "palivizumab" was known in the art as the generic term for SYNAGIS®, as indicated at page 1863 of the 2001 Physicians Desk Reference attached hereto as Exhibit D, Applicants maintain that it is proper to use the term "palivizumab" in claim 107.

Accordingly, Applicants maintain that claims 87, 91, 93, 94, and 95-116 satisfy the requirements of 35 U.S.C. §112, first paragraph, and respectfully request that this rejection be withdrawn.

CONCLUSION

Applicants believe that the present claims meet all of the requirements for patentability. Entry and consideration of the foregoing amendments and remarks into the file of the subject application is respectfully requested.

If a telephone interview would be of assistance in advancing prosecution of the subject application, Applicants' undersigned attorney invites the Examiner to telephone her at the number provided below.

Respectfully submitted,

Date: April 18, 2005

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Kabat Database and its applications: 30 years after the first variability plot

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ABSTRACT

The Kabat Database was initially started in 1970 to determine the combining site of antibodies based on the available amino acid sequences at that time. Bence Jones proteins, mostly from human, were aligned, using the now-known Kabat numbering system, and a quantitative measure, variability, was calculated for every position. Three peaks, at positions 24–34, 50–56 and 89–97, were identified and proposed to form the complementarity determining regions (CDR) of light chains. Subsequently, antibody heavy chain amino acid sequences were also aligned using a different numbering system, since the locations of their CDRs (31–35B, 50–65 and 95–102) are different from those of the light chains. CDRL1 starts right after the first invariant Cys 23 of light chains, while CDRH1 is eight amino acid residues away from the first invariant Cys 22 of heavy chains. During the past 30 years, the Kabat database has grown to include nucleotide sequences, sequences of T cell receptors for antigens (TCR), major histocompatibility complex (MHC) class I and II molecules and other proteins of immunological interest. It has been used extensively by immunologists to derive useful structural and functional information from the primary sequences of these proteins. An overall view of the Kabat Database and its various applications are summarized here. The Kabat Database is freely available at <http://immuno.bme.nwu.edu>

INTRODUCTION

The purpose of maintaining the Kabat Database of aligned sequences of proteins of immunological interest, in our opinion, is to provide useful correlations between structure and function for this special group of proteins from their nucleotide and amino acid sequences to their tertiary structures (1). These sequences are thus aligned with the ultimate aim of understanding how these proteins are folded and how they can perform their biological functions. We include only coding region sequences that have been published. In some cases, only the amino acid sequences were published, while the corresponding nucleotide sequences were deposited in GenBank. All stored

sequences were then printed out and checked visually against available published sequences. We routinely survey for possible new sequences in journals in our libraries, Medline entries, cross-references from other papers, and author notification; however, we may still miss some sequences. GenBank, on the other hand, contains a substantial number of unpublished sequences. If there are doubts about these sequences or their annotations, please refer to the original papers. The Kabat numbering systems (see the Introduction of 2) for antibody light and heavy chains, for TCR alpha and beta chains, etc., go hand-in-hand with variability calculations. The locations of the CDRs are the theoretically derived positions which can be verified experimentally. Indeed, from the first antigen-antibody Fab complex (3) to the complexes of TCR, processed peptide and MHC class I molecule (4,5), it has been realized that alignment of amino acid sequences and variability calculations can be of utmost importance in understanding how these important macromolecules function biologically. Due to the rapid development of genetic and protein engineering methods, mouse and rat antibodies have been humanized to treat human cancers, viral infections, etc (6). CDRs of selected rodent antibodies are cut out and glued onto human antibody frameworks to minimize rejection by human patients.

Our predicted CDRs are slightly different from Chothia's. A careful comparison can be found from a hyperlink on our website to 'Andrew's Antibody Page' (<http://www.biochem.ucl.ac.uk/~martin/abs/index.html>).

Massive amounts of sequence data are being continuously published in the scientific literature. It is imperative to collect and properly align the sequences so that they can be used by as many researchers in this field as possible. We have previously published five editions of these sequences (see the Introduction of 2). In 1991, the fifth edition (2) consisted of three volumes. Currently, the database is more than five times as large. As of September 29, 1999, the Kabat database contained 1 599 375 and 2 517 756 nt for antibody light and heavy chain variable regions, respectively, as compared to 272 244 and 418 962 nt in 1991. Total numbers of entries, amino acids and bases of other categories of sequences can be obtained by using the 'Current Counts' hyperlink on our website. The collection is available on our website (<http://www.immuno.bme.nwu.edu>) which is free due to the generous support by various research grants from NIH since 1970.

Finally, numerous scientific papers have cited our database, quoting our fourth edition (7), fifth edition (2), or one of our more recent papers (8). On our part, we have been analyzing

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the Kabat Database during the past few years with reference to the total numbers of antibody and TCR V-genes, possible evolutionary selection processes, importance of antibody CDRH3s as related to their fine specificities, etc.

KABAT DATABASE

The Kabat Database may be accessed for searching, sequence retrieval and analysis by a few different methods: electronic mail, WWW and ftp. The electronic mail interface has been available since 1993, the WWW interface since 1995 and various formats of the database in electronic format for nearly a decade (8). Our data formats, searching tools, output formats and database structures have gradually been adopted by other immunological databases and interfaces.

Electronic mail interface

An electronic mail interface (seqhnt2@immuno.bme.nwu.edu) provides a non-interactive method for searching and sequence retrieval (9). Sending mail to the server address with the single word 'help' (no quotes) in the message body returns instructions for using the server.

All sequences classes are searchable and returnable. The query format allows making AND/OR/NOT constructed restrictions on the database and amino acid and nucleotide sequence pattern matching with allowable differences. Requests are processed as they are received and depending on the network traffic, take ~1–2 min to be searched and returned to the sender. The returned format is a fixed-line length record of 80 or fewer characters per line for ease in visual inspection and processing by user-written scripts or programs. The characters are plain text.

The query format for the sent request consists of two parts. The first part contains directives for the server to follow while the second part contains specifications of the search. Specification of the extent of data returned, the number of documents to return, starting document and whether plain ASCII text or PostScript should be used in the return format may be entered. Further, one can direct the server to return a distribution, the variability or unaligned raw data for the search specified.

The second part of the query contains the search restrictions on the database. Words separated by AND and OR may be used, as well as searching functions, like nucleotide/amino acid pattern matching and positional restriction matching.

There are basically three steps in translating and performing a search on the Kabat Database: generate the question or query, translate it into a format the server can recognize and decide on the output options desired of the returned matches. For example, if matches of mouse kappa light chains of anti-phosphorylcholine antibodies are desired, the query and restriction on the database would be:

Begin

@mouse and kappa and phosphorylcholine

The '@' before mouse tells the server that matches of the species mouse are desired, rather than searching through the entire database record for instances of the word 'mouse'. More complicated restrictions can be generated using parentheses for grouping and the minus sign '-' for NOT. Finding all rat and rabbit sequences which are not kappa light chains, and returning them as amino acid sequences in PostScript format would be constructed as:

PSAA

Begin

(rat and rabbit) and -kappa

Pattern matching is interpreted as the second part of an AND statement, such that finding all rat and rabbit sequences which are not kappa and contain the nucleotide pattern cagtacgtcag with three allowable mismatches, would be sent as:

Begin

(rat and rabbit) and -kappa [implicit AND]

#NM 3

cagtacgtcag

More examples of searching and output options may be found in the 'help' file returned from the server.

WWW interface

The WWW interface (8) to the Kabat Database: <http://immuno.bme.nwu.edu> contains searching and analysis tools as well as links to database download sites and other interesting databases. Most of the features found in the electronic mail interface are found in the WWW interface, as well as other tools. The WWW interface is more interactive than the Email and returns results faster, depending on the network traffic.

Searching and analysis tools

SeqhntII. This grouping of programs allows searches through the annotations and sequence pattern matching of the amino acid and nucleotide sequence data with allowable mismatches. Like the Email server, restrictions on the database may be formulated as AND/OR/NOT constructs. Output extent, output format, maximum documents and starting document may be specified. Browsing of the output results in HTML format allows the user to view the database entries in an easy-to-read format. ASCII text may be selected as output for use in user-generated scripts and programs. PostScript generation allows for printing on a PostScript supporting printer. Sequence matching is returned aligned with the target sequence with nucleotide or amino acid differences from the database sequence displayed in a case change. Since the database contains only coding regions of genes and proteins, the query sequence should be a portion of the coding region being sought.

Variability. Variability and amino acid distributions of sequence groups may be generated for restrictions on the database. The variability plots are in PostScript format and may either be viewed on the screen with an appropriate PostScript viewer (e.g. GNU ghostscript or ghostview) or printed to a postscript-supporting printer. Plots for human and mouse TCR gamma and delta chain variable regions are shown in Figure 1. Scaling of the variability plots may be done allowing comparison of variability plots for different groupings of sequences. Distributions of the amino acids per position may be returned also, including the calculated variability for each position.

Sequence alignment. Alignment of user-entered coding regions of immunoglobulin light chains according to the Kabat numbering system can be performed. Because of the relatively few alignment options available for light chains, most sequences can be aligned. One can start with around 10 amino acid residues or 30 nt. There is no lower limit on the length of sequence to be matched. In some cases though, visual inspection and alignment is necessary, as is for heavy chain alignment,

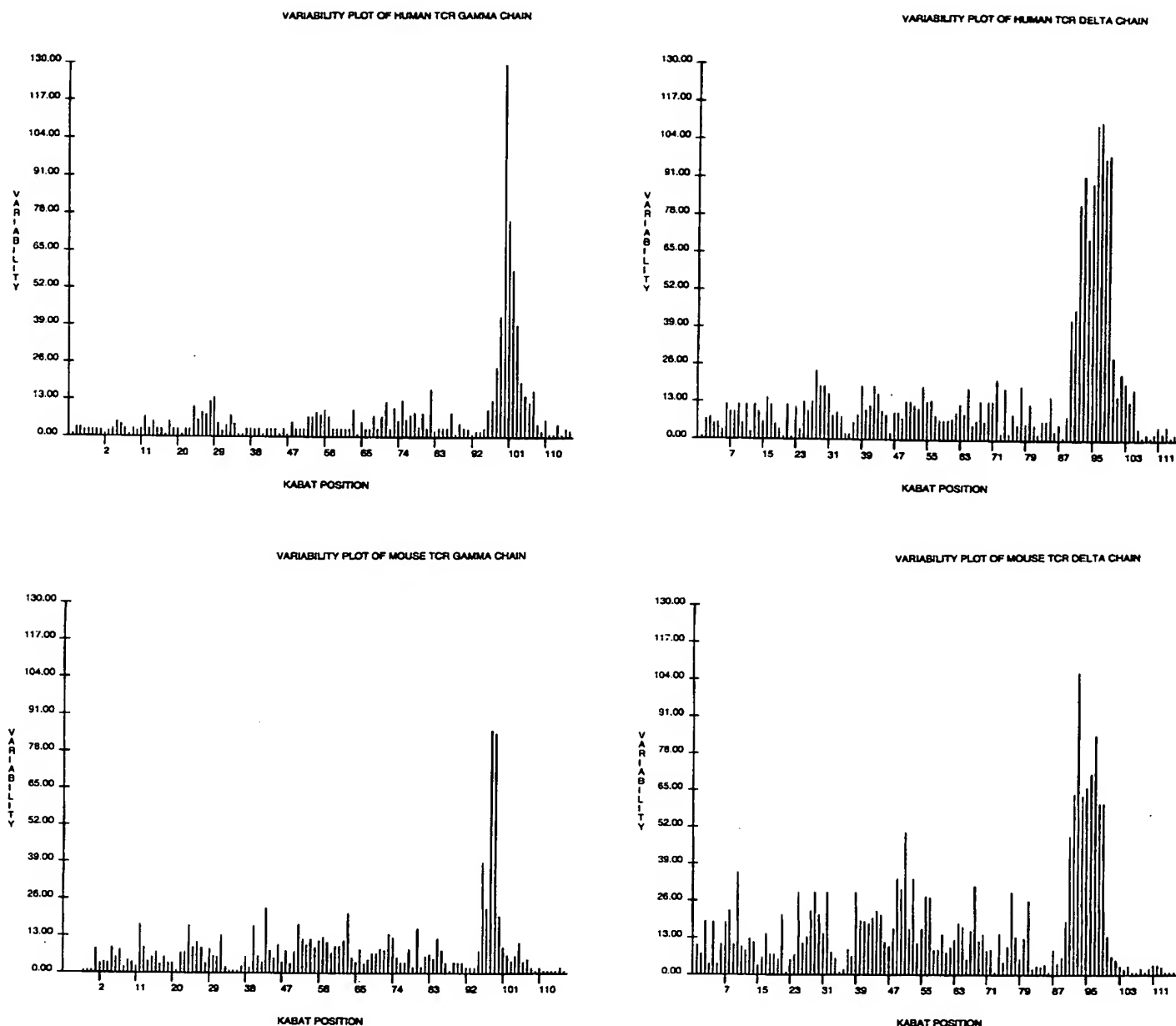


Figure 1. Variability plots for human and mouse TCR gamma and delta chain variable regions, using 377 human gamma, 1260 human delta, 297 mouse gamma and 461 mouse delta partial and complete sequences.

especially within the CDRH3 region, if additional codons or residues are inserted and denoted by '#'. If a suitable alignment counterpart from the database is not found for the target sequence, the user can contact us.

FTP. Various formats of the database are available for download from NCBI's repository under the directory 'kabat'. Currently active formats include a FASTA-like raw sequence format and the database's fixed length format of 80 or fewer

characters per line and vertical alignment. Four main variations on the fixed length format exist to properly visually display single translations, pseudogene translations, J-minigenes and D-minigenes. Other immunological databases have adopted similar formats as exemplified by the three letter code amino acid translation followed by single letter code. A 'dump' version of the database is periodically updated which contains unlimited line length records more suitable for mass processing on unix-based systems.

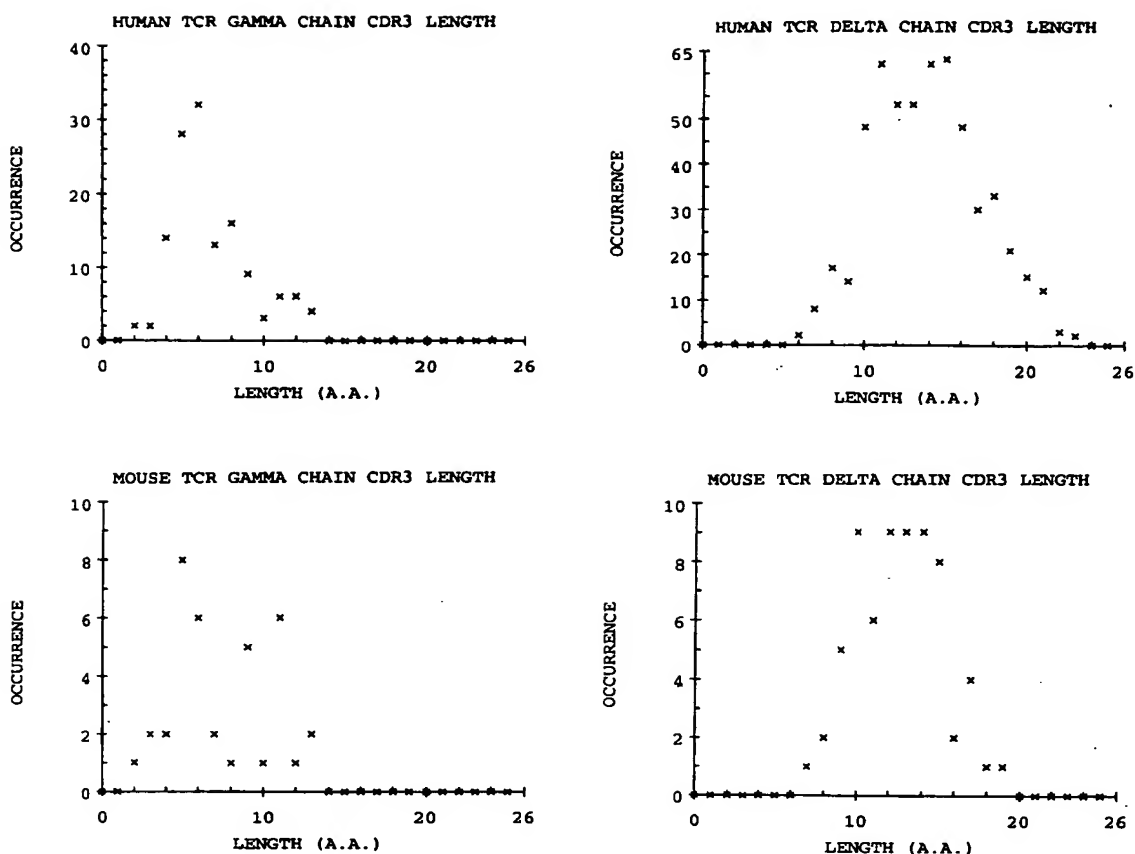


Figure 2. Length distributions of CDR3s of human and mouse TCR gamma and delta chains, based on 135 human gamma, 546 human delta, 37 mouse gamma and 66 mouse delta complete CDR3 sequences.

OTHER APPLICATIONS

As mentioned before, the Kabat Database was initially constructed for the purpose of identifying the antibody combining site (1). Starting from aligned amino acid sequences and using variability calculations, we have identified CDRs of antibody light and heavy chains, as well as those of TCRs. Such calculations can also provide useful predictions for MHC class I and II sequences (8), and to other aligned proteins sequences, e.g. HIV gp120, gp41, etc.

The importance of CDRH3 to confer fine specificity to antibodies was realized a few years ago (10). Furthermore, the unique CDRH3 nucleotide sequences have recently been used as a sensitive diagnostic test to detect residue B cell malignancies in cancer patients. Thus, many of these sequences have been determined. But most of them have been excluded from GenBank due to their relative short lengths. We have been meticulously collecting them, and realized the importance of their length distributions in antibodies of various specificities (11), and possible differences between CDRH3s of human and mouse (12). In the case of rabbit, the CDRH3s have less length variation than human and mouse. This may be compensated by the length variations of the CDRL3s (13).

The length variations of TCR alpha and beta chain CDR3s are very restricted (14). On the other hand, TCR gamma and delta chain CDR3s have more length variation, close to those of antibody heavy chains (Fig. 2). Whether they bind antigens directly is unclear.

During recent years, various research groups have decided to sequence the entire coding region of different antibody and TCR V-genes, in order to have an idea of their total numbers. On the other hand, we have discovered that pair-wise comparisons of V-gene nucleotide sequences in the Kabat Database provide very accurate estimations of their total numbers (15,16). In addition, such comparisons seem to suggest that antibody and TCR V-genes have evolved under different selective pressures (17). In the case of MHC class I sequences, comparison of their aligned sequences has elucidated a new mechanism of generating novel MHC class I molecules by random assortment of their $\alpha 1$ and $\alpha 2$ gene segments (18).

DISCUSSION

The Kabat Database has been around for 30 years. It has provided the immunology community a useful service, since it

not only is a sequence database but also incorporates vital aspects of the biology of the immune system. Various analytical methods have been developed to study the structure and function relations of proteins of immunological interest.

Electronic addresses:

<http://immuno.bme.nwu.edu>

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In Fig. 1 and in the stereomodels of antibody combining sites, the location of the allotypic regions may clearly be seen to be on the outside of V_H away from the combining site. Residues 9 and 65 of V_H are numbered and will facilitate location of the V_H allotypes. The few cDNA sequences available in 1984 (65) provided no evidence that germ line sequences encoding latent allotypes may exist in some rabbits. Since then, additional germline and expressed V_H sequences (63-65, 188, 204-206) have further refined the information on V_H allotypes and V_H sequences. Newer analyses of germline V_H genes of rabbits have provided examples of potential genes and pseudogenes which could generate latent allotype sequences by somatic gene conversion mechanisms (187, 199, 203-208). Antisera to rabbit V_H allotypes crossreact with human IgG, various other species of IgM and IgG, and with the Galapagos shark 7S immunoglobulin and correlate with the N-terminal amino acid sequence (209, 210).

It is becoming of great importance, with all of the different mechanisms which are clearly generating diversity, to evaluate the extent to which each type of diversity, other than those resulting in pseudogenes, contributes noise rather than functional differences in complementarity of antibody combining sites (70, 211).

Ohno et al. (212, 213) have proposed that the genes coding for variable domains of the light and heavy chains arose from tandem repeats of a primordial nucleotide sequence about 48 base pairs in length which subsequently diverged by mutations and deletions producing a resemblance to FR1, FR2, and FR3. The complementary strand of the primordial 48 base pair repeat of V_L became the primordial V_H . The finding (147) that the complementary strands of the human D2 and D4 minigenes coded for a portion of CDR1 of V_L tends to support this hypothesis. A 45 base pair primordial building block has also been proposed for the gene for the class I major histocompatibility complex (214).

The format of our precursor, V-region, C region sequences etc. of antibodies and T cell receptors has proven very useful in selecting primers for the polymerase chain reaction (215-217).

Constant Region Sequences

The constant region sequences were aligned in such a manner as to permit various comparisons of the light chain (C_L) and the individual domains of the heavy chain (C_H1 , C_H2 , C_H3 , and C_H4). This was accomplished by sequential numbering on the left with gaps inserted for alignment. The following numbering system is used:

108 to 215 of C_L ;
114 to 223 of C_H1 , plus the first part of hinge (224 to 241),
the end of hinge (242 and 243), and the
first two residues of CH2 (244 and 245);
246 to 360 of C_H2 ;
361 to 496 of C_H3 ;
497 to 628 of C_H4 .

The gene quadruplication in the human IgG3 hinge region (218) is numbered differently using letters 241A to 241Z, and 241AA to 241SS, and these residues should not be used in aligning domains for homology. The next two columns in the heavy chain tables indicate the EU (67) and OU (219) residue numbers, respectively. The succeeding columns which are numbered give the sequence data. The C_H and hinge domains conform to the findings of Sakano et al. (220), who defined each domain precisely by sequencing the coding and intervening nucleotide sequences bordering each domain.

The extensive nucleotide sequence data on exons for the constant regions of heavy chains have provided exact boundaries for C_H1 , hinge, C_H2 , C_H3 , and C_H4 . Usually the introns separating these domains fall within the codon for a single amino acid. We have included that amino acid residue with the domain, the exon of which contains two of the three coding nucleotides. The constant regions

of heavy chains thus contain four domains: C_H1, hinge, C_H2, and C_H3, or in IgM and IgE C_H1, C_H2, C_H3, and C_H4. Several C_H3 domains are extra long. These have been listed in a separate table after C_H3. An additional table is included to list several C_H4 domains that are very long and the C-terminal portions of membrane bound segments. Such extra long sequences in C_H3, C_H4, and membrane bound segments are listed retaining their individual protein numbers.

There are substantial species differences between the human, rat and rabbit C_κ allotypes. The amino acid sequences of rabbit C_κ allotypic determinants K-1, b4, b5 and b9 differ at 47 of 106 positions, the differences occurring in clusters; the K-2bas isotype differs at three additional positions (221) whereas the human C_κ allotypes differ by two positions (222) and the rat R1-1a and R1-1b differ at 11 positions (223).

The Fc receptors (224,225) are members of the immunoglobulin superfamily and provide the mechanism for interactions involving the constant regions of immunoglobulins binding to both immune complexes and antibodies (226-232). There are receptors for all classes which have arisen from a common precursor to diversify functionally. Fc receptors for a given Ig may have different affinities; thus there are high and low affinities for IgE. Fc RI and FcRIII have been shown to consist of non covalently associated complexes (cf. 224-225).

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KAPPA LIGHT CONSTANT CHAINS (cont'd)

64 HORNED SHARK 1122 CL	65 1X1g31 CL 0	# OF SEQUENCES	# OF AMINO ACIDS	OCCURRENCES OF MOST COMMON AMINO ACID	VARIABILITY
107A	---	---	---	---	---
108A	---	---	---	---	---
109	SER	ASN	60	5	20 (ARG)
109A	GLU	---	8	2	29 (ALA)
110	ASP	ASP	58	5	4 (+)
111	ARG	ALA	57	5	25 (ASP), 21 (ASP)
112	LYS	LYS	58	4	34 (ALA)
113	PRO	PRO	59	2	52 (ALA)
114	SER	ALA	59	4	58 (PRO)
115	VAL	VAL	59	1	37 (THR)
116	LEU	PHE	59	3	59 (VAL)
117	LEU	ILE	59	2	24 (LEU)
118	LEU	PHE	59	3	46 (ILE)
119	PRO	LYS	59	3	35 (PHE)
120	PRO	PRO	59	1	57 (PRO)
121	SER	SER	59	2	54 (SER)
122	SER	ASP	60	9	24 (SER)
123	GLU	GLU	60	3, 4	44 (GLU), 39 (GLU)
124	---	---	60	4	45 (GLN), 40 (GLN)
124A	---	---	---	---	---
125	ILE	VAL	60	4	51 (LEU)
126	ASP	LYS	60	5	23 (THR)
127	SER	GLU	60	5	28 (+)
128	GLY	GLY	59	2, 3	55 (GLY)
129	TRP	ASN	60	7	29 (THR)
130	ALA	PRO	60	3	48 (ALA)
131	THR	THR	60	2	33 (SER)
132	LEU	ALA	58	2	34 (VAL)
133	SER	VAL	59	2	56 (VAL)
134	CYS	CYS	61	1	61 (CYS)
135	LEU	LEU	60	4	20 (+)
136	VAL	ILE	62	4	22 (LEU)
137	SER	ASN	61	3	56 (ASN), 55 (ASN)
138	ARG	ASN	61	6	33 (ASN), 31 (ASN)
139	PHE	PHE	63	2	50 (PHE)
140	LYS	PHE	62	4	42 (TYR)
141	PRO	PRO	63	1	63 (PRO)
142	GLY	ARG	64	6	22 (ARG)
143	PHE	ASP	64	5, 6	36 (ASP), 33 (ASP)
144	VAL	LEU	51	4	35 (ILE)
145	ARG	THR	64	2	23 (THR)
146	VAL	VAL	64	2	63 (VAL)
147	---	---	---	---	---
148	LEU	THR	62	4	26 (LYS)
149	TRP	TRP	62	1	62 (TRP)
150	VAL	VAL	61	2	51 (LYS)
151	---	---	---	---	---
152	ASP	ASP	61	2	60 (ASP), 58 (ASP)
153	LYS	GLN	58	7	42 (GLY)
154	GLU	ASP	59	6, 7	19 (SER)
155	THR	VAL	59	6, 7	28 (GLU), 26 (GLU)
156	ASP	SER	57	6	27 (GLN), 26 (GLN)
157	SER	SER	59	5	24 (GLN), 22 (GLN)
158	GLY	SER	60	4	20 (ASN), 14 (SER)
159	VAL	ASP	50	4	43 (GLY)
160	THR	VAL	58	6	28 (VAL)
161	GLY	THR	59	5, 6	24 (LEU)
162	THR	SER	54	6, 7	29 (ASN), 25 (ASN)
163	VAL	ASP	55	3	51 (SER)
164	SER	PHE	55	3	23 (VAL)
165	THR	MET	55	4, 5	51 (THR)
166	ASP	GLN	57	4	21 (ASP), 19 (PRO)
167	SER	GLU	56	4	49 (GLN), 45 (GLN)
168	ASP	SER	56	4	38 (ASP), 34 (ASP)
169	LEU	ASP	59	5	44 (SER)
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1. Petition for Extension of Time Under 37 CFR Section 1.136(a) (in duplicate);
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3. Amendment Under 37 C.F.R. Section 1.111;
4. A copy of the Information Disclosure Statement;
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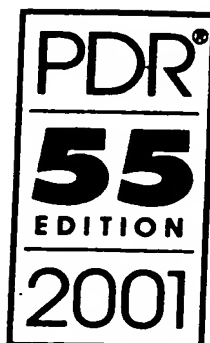
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Total Quantity of
Immunoglobulin
1000 mg \pm 200 mg
2500 mg \pm 500 mg

Volume
20 ml
50 ml

Concentration
50 \pm 10 mg/ml
50 \pm 10 mg/ml

SYNAGIS®
(palivizumab)
for Intramuscular Administration

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clinical experience with... suggests that the major... related to volume overload.

ADMINISTRATION

total dosage per infusion is... according to the following

Preparation

Remove the tab portion of... rubber stopper with 70% alcohol... VIAL; AVOID FOAMING. The... should be inspected visually for... prior to administration... permit. Infuse the solution... particulate matter and not tur-

begin within 6 hours after enter-... complete within 12 hours of en-... should be taken preinfusion, mid-... well as before any rate increase. The... through an intravenous... that contains an in-line fil-... infusion pump (i.e., IVAC... in-line filter (0.2 μ) is also... before infusion is not

through a separate in-... possible, CytoGam® may be... line if that line contains... USP, or one of the follow-... without NaCl added): 2.5%... in water, 10% dextrose in... If a pre-existing line must be... not be diluted more than 1:2... solutions. Admixtures of Cy-... have not been evaluated. In-... at 15 mg Ig per kg... reactions occur after 30... to 30 mg Ig/kg/hr; if no... 30 minutes, then... 60 mg Ig/kg/hr (volume not... EXCEED THIS RATE OF... should be monitored... into change.

at 15 mg Ig/kg/hr for 15... occur, increase to 30 mg... then increase to a maximum... not to exceed 75 ml/hour).
RATE OF ADMINISTRATION.
closely during each rate

with caution in patients with... and in patients judged to be... renal insufficiency (includ-... with diabetes mellitus, age... time, paraproteinemia, sepsis... nephrotic drugs). In these... to ensure that patients are... to CytoGam® infusion. While... have occurred in patients... Ig/kg or greater, no prospec-... to identify a maximum safe... of infusion in patients deter-... of acute renal failure. In the... recommended doses should not... and infusion rate se-... practicable. The product... of 150 mg Ig/kg/hr or less.

or: flushing, chills, muscle... vomiting, wheezing, drop... reactions have been in-... develops a minor side ef-... (flushing), slow the rate or tem-... If anaphylaxis or drop in... infusion and use antidote... and adrenalin.

of hepatitis viruses or other in-... to another, sterile dispos-... should be used. The syringes and

Immune Globulin Intrave-... to two single-dose vial forms:

between 2° C and 8° C (35.6° F... within 6 hours after entering the

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24. Scribner C, Kapit R, Philips E, et al. Aseptic meningitis and intravenous immunoglobulin therapy. *Ann Intern Med*; 121:305-306, 1994.

For additional information concerning Cytomegalovirus Immune Globulin Intravenous (Human) contact:

Professional Services

MedImmune, Inc.
35 West Watkins Mill Road
Gaithersburg, MD 20878, USA
1-800-949-3789

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Marketed by:
MedImmune Inc.
35 W. Watkins Mill Road
Gaithersburg, MD 20878
Revised April 2000

Shown in Product Identification Guide, page 323

DESCRIPTION

Synagis® (palivizumab) is a humanized monoclonal antibody (IgG1 κ) produced by recombinant DNA technology, directed to an epitope in the A antigenic site of the F protein of respiratory syncytial virus (RSV). Palivizumab is a composite of human (95%) and murine (5%) antibody sequences. The human heavy chain sequence was derived from the constant domains of human IgG1 and the variable framework regions of the V μ genes Cor (1) and Cess (2). The human light chain sequence was derived from the constant domain of C κ and the variable framework regions of the V λ gene K104 with J κ -4 (3). The murine sequences were derived from a murine monoclonal antibody, Mab 1129 (4), in a process which involved the grafting of the murine complementarity determining regions into the human antibody framework. Synagis® is composed of two heavy chains and two light chains and has a molecular weight of approximately 148,000 Daltons.

Synagis® is supplied as a sterile lyophilized product for reconstitution with sterile water for injection. Reconstituted Synagis® is to be administered by intramuscular injection only. Upon reconstitution, Synagis® contains the following excipients: 47 mM histidine, 3.0 mM glycine and 5.6% mannitol and the active ingredient, palivizumab, at a concentration of 100 milligrams per vial. The reconstituted solution should appear clear or slightly opalescent.

CLINICAL PHARMACOLOGY

Mechanism of Action: Synagis® exerts neutralizing and fusion-inhibitory activity against RSV. These activities inhibit RSV replication in laboratory experiments. Although resistant RSV strains may be isolated in laboratory studies, a panel of 57 clinical RSV isolates were all neutralized by Synagis® (5). Synagis® serum concentrations of ≥ 40 μ g/ml have been shown to reduce pulmonary RSV replication in the cotton rat model of RSV infection by 100-fold (5). The *in vivo* neutralizing activity of the active ingredient in Synagis® was assessed in a randomized, placebo-controlled study of 35 pediatric patients tracheally intubated because of RSV disease. In these patients, palivizumab significantly reduced the quantity of RSV in the lower respiratory tract compared to control patients (6).

Pharmacokinetics: In studies in adult volunteers Synagis® had a pharmacokinetic profile similar to a human IgG1 antibody in regard to the volume of distribution and the half-life (mean 18 days). In pediatric patients less than 24 months of age, the mean half-life of Synagis® was 20 days and monthly intramuscular doses of 15 mg/kg achieved mean \pm SD 30 day trough serum drug concentrations of 37 ± 21 μ g/mL after the first injection, 57 ± 41 μ g/mL after the second injection, 68 ± 51 μ g/mL after the third injection and 72 ± 50 μ g/mL after the fourth injection (7). In pediatric patients given Synagis® for a second season, the mean \pm SD serum concentrations following the first and fourth injections were 61 ± 17 μ g/mL and 86 ± 31 μ g/mL, respectively.

CLINICAL STUDIES

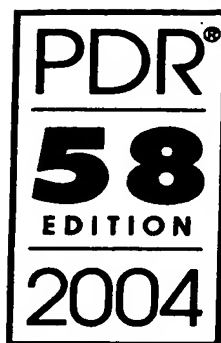
The safety and efficacy of Synagis® were assessed in a randomized, double-blind, placebo-controlled trial (IMPACT-RSV Trial) of RSV disease prophylaxis among high-risk pediatric patients (7). This trial, conducted at 139 centers in the United States, Canada and the United Kingdom, studied patients ≤ 24 months of age with bronchopulmonary dysplasia (BPD) and patients with premature birth (≤ 35 weeks gestation) who were ≤ 6 months of age at study entry. Patients with uncorrected congenital heart disease were excluded from enrollment. In this trial, 500 patients were randomized to receive five monthly placebo injections and 1,002 patients were randomized to receive five monthly injections of 15 mg/kg of Synagis®. Subjects were randomized into the study from November 15 to December 13, 1996, and were followed for safety and efficacy for 150 days. Ninety-nine percent of all subjects completed the study and 93% received all five injections. The primary endpoint was the incidence of RSV hospitalization.

RSV hospitalizations occurred among 53 of 500 (10.6%) patients in the placebo group and 48 of 1002 (4.8%) patients in the Synagis® group, a 55% reduction ($p < 0.001$). The reduction of RSV hospitalization was observed both in patients enrolled with a diagnosis of BPD (34/266 [12.8%] placebo vs 39/496 [7.9%] Synagis®) and patients enrolled with a diagnosis of prematurity without BPD (19/234 [8.1%] placebo vs 9/506 [1.8%] Synagis®). The reduction of RSV hospitalization was observed throughout the course of the RSV season. Among secondary endpoints, the incidence of ICU admission during hospitalization for RSV infection was lower among subjects receiving Synagis® (1.3%) than among those receiving placebo (3.0%), but there was no difference in the mean duration of ICU care between the two groups for patients requiring ICU care. Overall, the data do not suggest that RSV illness was less severe among patients who received Synagis® and who required hospitalization due to RSV infection than among placebo patients who required hospitalization due to RSV infection. Synagis® did not alter the incidence and mean duration of hospitalization for non-RSV respiratory illness or the incidence of otitis media.

Continued on next page

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Total Quantity of Immunoglobulin	Volume	Concentration
1000 mg \pm 200 mg	20 ml	50 \pm 10 mg/ml
2500 mg \pm 500 mg	50 ml	50 \pm 10 mg/ml

Signs should be taken preinfusion, mid-infusion as well as before any rate increase. Administer through an intravenous infusion set that contains an in-line filter and a constant infusion pump (i.e., IVAC). A smaller in-line filter (0.2 μ) is also available. CytoGam $\text{\textcircled{R}}$ before infusion is not recommended. CytoGam $\text{\textcircled{R}}$ should be administered through a "piggybacked" into a pre-existing line if either Sodium Chloride, Injection, USP, or 5% dextrose solutions (with or without 5% dextrose in water, 5% dextrose in water, 20% dextrose in water. If a pre-existing line with any of the above-named solutions, CytoGam $\text{\textcircled{R}}$ with any other solutions have not

Administer intravenously at 15 mg Ig per kg per hour. If no adverse reactions occur after 30 minutes may be increased to 30 mg Ig/kg/hr; if no adverse reactions occur after a subsequent 30 minutes, then may be increased to 60 mg Ig/kg/hr (volume not to exceed 1800 ml). DO NOT EXCEED THIS RATE OF INFUSION. The patient should be monitored after each rate change.

Administer at 15 mg Ig/kg/hr for 15 minutes. If adverse reactions occur, increase to 30 mg Ig/kg/hr and then increase to a maximum of 60 mg Ig/kg/hr (volume not to exceed 1800 ml). DO NOT EXCEED THIS RATE OF ADMINISTRATION. Should be monitored closely during each rate

Cytomegalovirus Immune Globulin Intravenous (CMV-IGIV), should be used with caution in patients with pre-existing renal insufficiency and in patients at increased risk of developing renal impairment, but not limited to those with diabetes mellitus, patients receiving known nephrotoxic drugs, and patients receiving known nephrotoxic drugs. It is important to assure that volume depletion prior to CytoGam $\text{\textcircled{R}}$ has been corrected. In most cases of renal insufficiency have patients receiving total doses of 400 mg Ig/kg or less. If patients are presently available to identify renal function, concentration or rate of infusion should be determined to be at increased risk of acute renal failure. In the absence of prospective data, recommended infusion rate should be the minimum practicable. CytoGam $\text{\textcircled{R}}$ should be infused at a rate of 180 mg Ig/kg/hr

Adverse reactions are: flushing, chills, muscle aches, fever, nausea, vomiting, wheezing, drop in blood pressure. Minor adverse reactions have been infrequent. If the patient develops a minor side effect (back pain, flushing), slow the rate or temporarily stop the infusion. If anaphylaxis or drop in blood pressure, discontinue infusion and use antihistamines and epinephrine.

The transmission of hepatitis viruses or other infections from one person to another, sterile disposable needles should be used. The syringes and needles should be reused.

Cytomegalovirus Immune Globulin Intravenous (CMV-IGIV) is supplied in two single-dose vial forms:

It should be stored between 2 $^{\circ}$ C and 8 $^{\circ}$ C (35.6 $^{\circ}$ F to 46.4 $^{\circ}$ F) and used within 6 hours after entering the

Proceed 26, suppl 1:23-27, 1994. 9. Merigan TC, Renlund DG, Keay S et al. A controlled trial of ganciclovir to prevent cytomegalovirus disease after heart transplantation. *NEJM* 326:1182-1186, 1992. 9. Ham JM, Shelden SR, Godkin RR, et al. Cytomegalovirus prophylaxis with ganciclovir, acyclovir and CMV hyperimmune globulin in liver transplant patients receiving OKT3 induction. *Transplant Proc*; 27 (5 Suppl 1):31-33, 1995. 10. Snyderman DR. Combined CMV-IGIV and ganciclovir prophylaxis in CMV seronegative transplant recipients from CMV seropositive donors. Report on file, MedImmune, Inc. 11. Martin M. CMV prophylaxis with combination ganciclovir and CMV hyperimmune globulin followed by high-dose acyclovir in solid organ transplant recipients. Report on file, MedImmune, Inc. 12. Valantine H and Luikart H. Impact of CMV hyperimmune globulin on outcome after cardiopulmonary transplantation: A comparative study of combined prophylaxis with CMVIG plus ganciclovir vs. ganciclovir alone. Report on file, MedImmune, Inc. 13. Bossell, et al. Safety of therapeutic immune globulin preparations with respect to transmission of human T-lymphotropic virus type III/lymphadenopathy-associated virus infection. *MMWR* vol. 35:231-233, April 11, 1996. 14. Wells MA, Wittek AE, Epstein JS, et al. Inactivation and partition of human T-cell lymphotropic virus, type III, during ethanol fractionation of plasma. *Transfusion* 28:210-213, 1988. 15. McIver J, Grady G. Immune globulin preparations. In: Churchill WH and Kurtz SR, (ed): *Transfusion Medicine*. Boston: Blackwell; 1988. 16. Schneider L, Geha R. Outbreak of Hepatitis C associated with intravenous immunoglobulin administration—United States, October 1993–June 1994. *MMWR* vol. 43:506–509, July 22, 1994. 17. Edwards CA, Piet MPJ, Chin S, et al. Tri(nButyl) phosphate detergent treatment of licensed therapeutic and experimental blood derivatives. *Vox Sang* 52:53–59, 1987. 18. Cayco AV, Perazella MA, Hayslett JP. Renal insufficiency after intravenous immune globulin therapy: A report of two cases and an analysis of the literature. *J Am Soc Nephrol*; 8: 1788–1793, 1997. 19. Cantu TG, Hoeft-Saric EW, Burgess KM et al. Acute renal failure associated with immunoglobulin therapy. *Am J Kidney Dis*; 25: 228–234, 1995. 20. Hansen-Schmidt S, Silomon J, Keller F. Osmotic nephrosis due to high-dose immunoglobulin therapy containing sucrose (but not with glycine) in a patient with immunoglobulin A nephritis. *Am J Kidney Dis*; 28: 451–453, 1996. 21. Sekul E, Culper E, Dalaks M. Aseptic meningitis associated with high-dose intravenous immunoglobulin therapy: Frequency and risk factors. *Ann Int Med*; 121:259–262, 1994. 22. Kato E, Shindo S, Eto Y, et al. Administration of immune globulin associated with aseptic meningitis. *JAMA*; 259:3269–3270, 1988. 23. Casteels Van Daele M, Wijnandse L, Hunnicke K, et al. Intravenous immunoglobulin and acute aseptic meningitis. *NEJM*; 323:614–615, 1990. 24. Scribner C, Kapit R, Philips E, et al. Aseptic meningitis and intravenous immunoglobulin therapy. *Ann Intern Med*; 121:305–306, 1994.

For additional information concerning Cytomegalovirus Immune Globulin Intravenous (Human) contact: Professional Services MedImmune, Inc. 35 West Watkins Mill Road Gaithersburg, MD 20878, USA 1-800-949-3789 Manufactured by: MASSACHUSETTS PUBLIC HEALTH BIOLOGIC LABORATORIES Boston, Massachusetts 02130, USA U.S. Govt. License No. 64 Marketed by: MedImmune, Inc. 35 West Watkins Mill Road Gaithersburg, MD 20878 Revised April 2000

Shown in Product Identification Guide, page 324

SYNAGIS $\text{\textcircled{R}}$ (palivizumab) (palivizumab) for Intramuscular Administration

DESCRIPTION

Synagis $\text{\textcircled{R}}$ (palivizumab) is a humanized monoclonal antibody (IgG1 κ) produced by recombinant DNA technology, directed to an epitope in the A antigenic site of the F protein of respiratory syncytial virus (RSV). Palivizumab is a composite of human (95%) and murine (5%) antibody sequences. The human heavy chain sequence was derived from the constant domains of human IgG1 and the variable framework regions of the V H genes Cor (1) and Cess (2). The human light chain sequence was derived from the constant domain of C κ and the variable framework regions of the V L gene K104 with J κ -4 (3). The murine sequences were derived from a murine monoclonal antibody, Mab 1129 (4), in a process which involved the grafting of the murine complementarity determining regions into the human antibody framework. Synagis $\text{\textcircled{R}}$ (palivizumab) is composed of two heavy chains and two light chains and has a molecular weight of approximately 148,000 Daltons.

Synagis $\text{\textcircled{R}}$ (palivizumab) is supplied as a sterile lyophilized product for reconstitution with sterile water for injection. Reconstituted Synagis $\text{\textcircled{R}}$ (palivizumab) is to be administered by intramuscular injection only. Upon reconstitution, Synagis $\text{\textcircled{R}}$ (palivizumab) contains the following excipients: 47 mM histidine, 3.0 mM glycine and 5.6% mannitol and the active ingredient, palivizumab, at a concentration of 100 milligrams per ml solution. The reconstituted solution should appear clear or slightly opalescent.

CLINICAL PHARMACOLOGY

Mechanism of Action: Synagis $\text{\textcircled{R}}$ (palivizumab) exhibits neutralizing and fusion-inhibitory activity against RSV. These activities inhibit RSV replication in laboratory experiments. Although resistant RSV strains may be isolated in laboratory studies, a panel of 57 clinical RSV isolates were all neutralized by Synagis $\text{\textcircled{R}}$ (palivizumab) (5). Synagis $\text{\textcircled{R}}$ (palivizumab) serum concentrations of \geq 40 μ g/ml have been shown to reduce pulmonary RSV replication in the cotton rat model of RSV infection by 100-fold (5). The *in vivo* neutralizing activity of the active ingredient in Synagis $\text{\textcircled{R}}$ (palivizumab) was assessed in a randomized, placebo-controlled study of 35 pediatric patients tracheally intubated because of RSV disease. In these patients, palivizumab significantly reduced the quantity of RSV in the lower respiratory tract compared to control patients (6). **Pharmacokinetics:** In studies in adult volunteers Synagis $\text{\textcircled{R}}$ (palivizumab) had a pharmacokinetic profile similar to a human IgG1 antibody in regard to the volume of distribution and the half-life (mean 18 days). In pediatric patients less than 24 months of age, the mean half-life of Synagis $\text{\textcircled{R}}$ (palivizumab) was 20 days and monthly intramuscular doses of 15 mg/kg achieved mean \pm SD 30 day trough serum drug concentrations of 37 \pm 21 μ g/ml after the first injection, 57 \pm 41 μ g/ml after the second injection, 68 \pm 51 μ g/ml after the third injection and 72 \pm 50 μ g/ml after the fourth injection (7). In pediatric patients given Synagis $\text{\textcircled{R}}$ (palivizumab) for a second season, the mean \pm SD serum concentrations following the first and fourth injections were 61 \pm 17 μ g/ml and 86 \pm 31 μ g/ml, respectively.

CLINICAL STUDIES

The safety and efficacy of Synagis $\text{\textcircled{R}}$ (palivizumab) were assessed in a randomized, double-blind, placebo-controlled trial (IMPACT-RSV Trial) of RSV disease prophylaxis among high-risk pediatric patients (7). This trial, conducted at 139 centers in the United States, Canada and the United Kingdom, studied patients \leq 24 months of age with bronchopulmonary dysplasia (BPD) and patients with premature birth (\leq 35 weeks gestation) who were \leq 6 months of age at study entry. Patients with uncorrected congenital heart disease were excluded from enrollment. In this trial, 500 patients were randomized to receive five monthly placebo injections and 1,002 patients were randomized to receive five monthly injections of 15 mg/kg of Synagis $\text{\textcircled{R}}$ (palivizumab). Subjects were randomized into the study from November 15 to December 13, 1998, and were followed for safety and efficacy for 150 days. Ninety-nine percent of all subjects completed the study and 93% received all five injections. The primary endpoint was the incidence of RSV hospitalization. RSV hospitalizations occurred among 53 of 500 (10.6%) patients in the placebo group and 48 of 1002 (4.8%) patients in the Synagis $\text{\textcircled{R}}$ (palivizumab) group, a 55% reduction ($p < 0.001$). The reduction of RSV hospitalization was observed both in patients enrolled with a diagnosis of BPD (34/266 [12.8%] placebo vs 39/496 [7.9%] Synagis $\text{\textcircled{R}}$ (palivizumab)) and patients enrolled with a diagnosis of prematurity without BPD (19/234 [8.1%] placebo vs 9/506 [1.8%] Synagis $\text{\textcircled{R}}$ (palivizumab)). The reduction of RSV hospitalization was observed throughout the course of the RSV season.

Among secondary endpoints, the incidence of ICU admission during hospitalization for RSV infection was lower among subjects receiving Synagis $\text{\textcircled{R}}$ (palivizumab) (1.3%) than among those receiving placebo (3.0%), but there was no difference in the mean duration of ICU care between the two groups for patients requiring ICU care. Overall, the data do not suggest that RSV illness was less severe among patients who received Synagis $\text{\textcircled{R}}$ (palivizumab) and who required hospitalization due to RSV infection than among placebo patients who required hospitalization due to RSV infection. Synagis $\text{\textcircled{R}}$ (palivizumab) did not alter the incidence and mean duration of hospitalization for non-RSV respiratory illness or the incidence of otitis media.

INDICATIONS AND USAGE

Synagis $\text{\textcircled{R}}$ (palivizumab) is indicated for the prevention of serious lower respiratory tract disease caused by respiratory syncytial virus (RSV) in pediatric patients at high risk of RSV disease. Safety and efficacy were established in infants with bronchopulmonary dysplasia (BPD) and infants with a history of prematurity (\leq 35 weeks gestational age). (See Clinical Studies section)

CONTRAINDICATIONS

Synagis $\text{\textcircled{R}}$ (palivizumab) should not be used in pediatric patients with a history of a severe prior reaction to Synagis $\text{\textcircled{R}}$ (palivizumab) or other components of this product.

WARNINGS

Very rare cases of anaphylaxis ($<$ 1 case per 100,000 patients) have been reported following re-exposure to Synagis $\text{\textcircled{R}}$ (palivizumab) (see Adverse Reactions, Post-Market-

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Continued on next page

ing Experience). Rare severe acute hypersensitivity reactions have also been reported on initial exposure or re-exposure to palivizumab. If a severe hypersensitivity reaction occurs, therapy with palivizumab should be permanently discontinued. If milder hypersensitivity reactions occur, caution should be used on readministration of palivizumab. If anaphylaxis or severe allergic reaction occurs, concomitant appropriate medications (e.g., epinephrine) and provide supportive care as required.

PRECAUTIONS

General: Synagis® (palivizumab) is for intramuscular use only. As with any intramuscular injection, Synagis® (palivizumab) should be given with caution to patients with thrombocytopenia or any coagulation disorder.

The safety and efficacy of Synagis® (palivizumab) have not been demonstrated for treatment of established RSV disease.

The single-use vial of Synagis® (palivizumab) does not contain a preservative. Injections should be given within 6 hours after reconstitution.

Drug Interactions: No formal drug-drug interaction studies were conducted. In the IMPact-RSV trial, the proportions of patients in the placebo and Synagis® (palivizumab) groups who received routine childhood vaccines, influenza vaccine, bronchodilators or corticosteroids were similar and no incremental increase in adverse reactions was observed among patients receiving these agents.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis, mutagenesis and reproductive toxicity studies have not been performed.

Pregnancy: Pregnancy Category C: Synagis® (palivizumab) is not indicated for adult usage and animal reproduction studies have not been conducted. It is also not known whether Synagis® (palivizumab) can cause fetal harm when administered to a pregnant woman or could affect reproductive capacity.

ADVERSE REACTIONS

In the combined pediatric prophylaxis studies of pediatric patients with BPD or prematurity involving 520 subjects receiving placebo and 1,168 subjects receiving 5 monthly doses of Synagis® (palivizumab), the proportions of subjects in the placebo and Synagis® (palivizumab) groups who experienced any adverse event or any serious adverse event were similar.

Most of the safety information was derived from the IMPact-RSV trial. In this study, Synagis® (palivizumab) was discontinued in five patients: two because of vomiting and diarrhea, one because of erythema and moderate induration at the site of the fourth injection, and two because of pre-existing medical conditions which required management (one with congenital anemia and one with pulmonary venous stenosis requiring cardiac surgery). Seizures were reported in 0.6% of the placebo group and 0.4% of the Synagis® (palivizumab) group. Deaths in study patients occurred in five of 500 placebo recipients and four of 1,002 Synagis® (palivizumab) recipients. Sudden infant death syndrome was responsible for two of these deaths in the placebo group and one death in the Synagis® (palivizumab) group. Adverse events which occurred in more than 1% of patients receiving Synagis® (palivizumab) in the IMPact-RSV study for which the incidence in the Synagis® (palivizumab) group was 1% greater than in the placebo group are shown in Table 1.

Table 1. Adverse Events Occurring in IMPact-RSV Study at Greater Frequency in the Synagis® (palivizumab) Group

% of patients with:	Placebo n = 500	Synagis® (palivizumab) n = 1,002
upper respiratory infection	49.0%	52.6%
otitis media	40.0%	41.9%
rhinitis	23.4%	28.7%
rash	22.4%	25.6%
pain	6.8%	8.5%
hernia	5.0%	6.3%
SGOT increased	3.8%	4.9%
pharyngitis	1.4%	2.6%

Other adverse events reported in more than 1% of the Synagis® (palivizumab) group included: fever, cough, wheeze, bronchiolitis, pneumonia, bronchitis, asthma, croup, dyspnea, sinusitis, apnea, failure to thrive, nervousness, diarrhea, vomiting, and gastroenteritis. SGPT increase, liver function abnormality, study drug injections site reaction, conjunctivitis, viral infection, oral monilia, fungal dermatitis, eczema, seborrhea, anemia and flu syndrome. The incidence of these adverse events was similar between the Synagis® (palivizumab) and placebo groups.

IMMUNOGENICITY: In the IMPact-RSV trial, the incidence of anti-palivizumab antibody following the fourth in-

jection was 1.1% in the placebo group and 0.7% in the Synagis® (palivizumab) group. In pediatric patients receiving Synagis® (palivizumab) for a second season, 0.6% of six patients had transient, low titer reactivity. This reactivity was not associated with adverse events or alterations in Synagis® (palivizumab) serum concentrations.

These data reflect the percentage of patients whose test results were considered positive for antibodies to Synagis® (palivizumab) in an ELISA assay, and are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to Synagis® (palivizumab) with the incidence of antibodies to other products may be misleading.

POST-MARKETING EXPERIENCE

The following adverse reactions have been identified and reported during post-approval use of Synagis® (palivizumab). Because the reports of these reactions are voluntary and the population is of uncertain size, it is not always possible to reliably estimate the frequency of the reaction or establish a causal relationship to drug exposure.

Based on experience in over 400,000 patients who have received Synagis® (palivizumab) (>2 million doses), rare severe acute hypersensitivity reactions have been reported on initial or subsequent exposure. Very rare cases of anaphylaxis (<1 case per 100,000 patients) have also been reported following re-exposure. None of the reported hypersensitivity reactions were fatal. Hypersensitivity reactions may include dyspnea, cyanosis, respiratory failure, urticaria, pruritis, angioedema, hypotonia and unresponsiveness. The relationship between these reactions and the development of antibodies to Synagis® (palivizumab) is unknown.

Limited information from post-marketing reports suggests that, within a single RSV season, adverse events after a sixth or greater dose of Synagis® (palivizumab) are similar in character and frequency to those after the initial five doses.

OVERDOSAGE

No data from clinical studies are available on overdosage. No toxicity was observed in rabbits administered a single intramuscular or subcutaneous injection of Synagis® (palivizumab) at a dose of 50 mg/kg.

DOSAGE AND ADMINISTRATION

The recommended dose of Synagis® (palivizumab) is 15 mg/kg of body weight. Patients, including those who develop an RSV infection, should receive monthly doses throughout the RSV season. The first dose should be administered prior to commencement of the RSV season. In the northern hemisphere, the RSV season typically commences in November and lasts through April, but it may begin earlier or persist later in certain communities.

Synagis® (palivizumab) should be administered in a dose of 15 mg/kg intramuscularly using aseptic technique, preferably in the anterolateral aspect of the thigh. The gluteal muscle should not be used routinely as an injection site because of the risk of damage to the sciatic nerve. The dose per month = (patient weight (kg) × 15 mg/kg + 100 mg/mL of Synagis® (palivizumab)). Injection volumes over 1 mL should be given as a divided dose.

Preparation for Administration

- To reconstitute, remove the tab portion of the vial cap and clean the rubber stopper with 70% ethanol or equivalent.
- Both the 50 mg and 100 mg vials contain an overfill to allow the withdrawal of 50 milligrams or 100 milligrams respectively when reconstituted following the directions described below.
- Slowly add 0.6 mL of sterile water for injection to the 50 mg vial or add 1.0 mL of sterile water for injection to the 100 mg vial. The vial should be gently swirled for 30 seconds to avoid foaming. DO NOT SHAKE VIAL.
- Reconstituted Synagis® (palivizumab) should stand at room temperature for a minimum of 20 minutes until the solution clarifies.
- Reconstituted Synagis® (palivizumab) does not contain a preservative and should be administered within 6 hours of reconstitution.

To prevent the transmission of hepatitis viruses or other infectious agents from one person to another, sterile disposable syringes and needles should be used. Do not reuse syringes and needles.

HOW SUPPLIED

Synagis® (palivizumab) is supplied in single use vials as lyophilized powder to deliver either 50 milligrams or 100 milligrams when reconstituted with sterile water for injection.

50 mg vial NDC 60574-4112-1
Upon reconstitution the 50 mg vial contains 50 milligrams Synagis® (palivizumab) in 0.5 mL.

100 mg vial NDC 60574-4111-1
Upon reconstitution the 100 mg vial contains 100 milligrams Synagis® (palivizumab) in 1.0 mL.

Upon receipt and until reconstitution for use, Synagis® (palivizumab) should be stored between 2 and 8°C (35.6 and 46.4°F) in its original container. Do not freeze. Do not use beyond the expiration date.

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Ethylol® (amifostine), see Listing under MedImmune Oncology, Inc.

ETHYOL®
(a-thiol)
AMIFOSTINE for Injection
Rx only.

DESCRIPTION

ETHYOL® (amifostine) is an organic thiophosphate ester, active agent known chemically as 2-[(3-aminopropyl)thio]ethanethiol dihydrogen phosphate (ester) and having the following structural formula:



Amifostine is a white crystalline powder which is freely soluble in water. Its empirical formula is $C_5H_{13}N_2O_3PS$ and has a molecular weight of 214.22.

ETHYOL® is the trihydrate form of amifostine and is supplied as a sterile lyophilized powder requiring reconstitution for intravenous infusion. Each single-use 10 mL vial contains 500 mg of amifostine on the anhydrous basis.

CLINICAL PHARMACOLOGY

ETHYOL® is a prodrug that is dephosphorylated by tissue phosphatases in tissues to a pharmacologically free thiol metabolite. This metabolite is believed to be responsible for the reduction of the cumulative toxicity of cisplatin and for the reduction of the toxic effects of cisplatin on normal oral tissues. The ability of ETHYOL® to preferentially protect normal tissues is attributed to its capillary alkaline phosphatase activity, higher pH in tumor vasculature of normal tissues relative to tumor tissues, which results in a more rapid generation of the active metabolite as well as a higher rate constant for uptake into cells. The higher concentration of the thiol metabolite in normal tissues is available to bind to, and thereby neutralize, reactive metabolites of cisplatin. This thiol metabolite also scavenges reactive oxygen species generated by cisplatin or radiation.

Pharmacokinetics: Clinical pharmacokinetic studies have shown that ETHYOL® is rapidly cleared from the plasma with a distribution half-life of <1 minute and an elimination half-life of approximately 15 minutes.